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INTERNAL DOSIMETRY INTAKE ESTIMATION USING BAYESIAN METHODS

by

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Summary

New methods for the inverse problem of internal dosimetry are proposed based on evaluating expectations of the Bayesian posterior probability distribution of intake amounts, given bioassay measurements. These expectation integrals are normally of very high dimension and hence impractical to use. However, the expectations can be algebraically transformed into a sum of terms representing different numbers of intakes, with a Poisson distribution of the number of intakes. This sum often rapidly converges, when the average number of intakes for a population is small. A simplified algorithm using data unfolding is described (UF code).

[0] *Key words*: internal dosimetry, intake estimation, Bayesian analysis, Bayesian posterior distributions, bioassay, internal dosimetry algorithms, Poisson process

1 Introduction

One goal of internal dosimetry is the determination of intakes of radioactive materials into the body from limited bioassay data. These data indicate the amount excreted from the body, for example, in urine. Given agreed-upon, forward, biokinetic models that summarize our scientific understanding of how the material passes through the body and imparts dose (e. g. ICRP publications 30, 54, and 66)[10][19][20], there remains a formidable inverse mathematical problem: given the amount excreted in urine as a function of time, determine the times, amounts, and types of intakes, including estimates of uncertainties. This generic type of linear, underdetermined, inverse problem with a positivity constraint is well suited to a Bayesian approach.

The causal character of the biokinetic response (excretion follows intake) allows simple unfolding techniques, which have been used exclusively in the past (see Lawrence, 1962, and Ward and Eckerman, 1992).[13, 26] Since excretion follows intake in time, intakes in a given sampling interval affect only subsequent urine excretion amounts and not urine excretion amounts preceding the intake. Thus, assuming an initial baseline bioassay sample and no preceding work history around the material, the second urine data value can be used to determine a possible intake in the first bioassay sampling interval (between the first and second samples). Calculated excretion resulting from this intake is subtracted from subsequent data values to determine possible subsequent intakes. These approaches suffer the criticism that the statistical significance of calculated intake amounts has not been calculated. The question of whether a calculated intake is real or statistically significant has not been addressed, except that negative calculated intakes are usually assumed to be not real (the linear unfolding techniques used so far allow negative intakes). In this paper we propose a Bayesian version of a data unfolding algorithm.

One of the problems of internal dosimetry is to select parameters of the biokinetic model (specifying the intake type) that "best describe" the data, given an agreed-upon model. This is equivalent to choosing the "best fit" model from a set of models calculated using different parameter values. Our methods incorporate the models as large, interpolated tables of excretions and organ doses versus time for unit intake; any set of linear models may be used as long as they adequately describe the possible patterns of excretion (by the principle of Occam's razor, one would choose the simplest such set of models that are otherwise satisfactory). In general, there will be a set of available biokinetic models distinguished by various parameter choices (for example, particle solubility in lung fluids and particle size, which determines the deposition pattern in the lung) as well as selecting qualitatively different models (such as the ^{238}Pu time-varying solubility model discussed in Appendix A). For our current calculations for occupational plutonium exposure, we use a set of models based on ICRP publication 30[10] since this is currently the basis of United States Department of Energy regulations. For ^{239}Pu inhalation intakes, we use 6 models

corresponding to 6 assumed intake types: class Y and class W with particle size 0.2 1.0 and 5 μm AMAD (a more detailed discussion of the biokinetic models we use for plutonium is given in the Appendix A). Default recommendations are generally given; for example, for plutonium the ICRP recommends that class Y, 1.0 μm AMAD be chosen in lieu of other information. For the same urine excretion, the choice of model can have a large effect on the calculated dose (for plutonium with a given urine excretion, the assumption of class W decreases the dose by about an order of magnitude relative to class Y). The internal dosimetry algorithm needs to take into account that different models are available with some being preferred. Also, the calculated uncertainties need to reflect this fact.

In a previous paper (Miller and Inkret, 1996),[17] we applied a well-known method in the field of radio-astronomy image reconstruction, the maximum entropy method (see Skilling, 1989),[22] to internal dosimetry. Using the maximum entropy method, intakes are necessarily positive and we are able to calculate the statistical uncertainty of intakes. However, the calculated intake scenarios tend to assign too many intakes to agree with our overall understanding and experience of how frequently acute intakes of this magnitude occur.

The problem with the maximum entropy method is the entropy form of the prior probability distribution. The entropy distribution is approximately exponential in the parameter range of interest and has a fixed value of the ratio of standard deviation to mean. To represent the probability distribution of radionuclide intakes into the body under typical conditions, the distribution needs to have a δ-function component representing "no intake". Distributions of this form can have an arbitrarily large value of the ratio of standard deviation to mean, unlike the entropy distribution, and they can be used as prior probability distributions to self consistently model situations where the observed frequency of intakes (population average) is small.

2 Bayesian Formulation of the Internal Dosimetry Problem

The current approach to internal dosimetry is to interpret bioassay measurements in terms of radionuclide intake amounts. Let x_i for $i = 1$ to N denote the amount of intake that occurred during time interval i, where N is the total number of time intervals. For example, in plutonium internal dosimetry x_i is the activity of plutonium taken into the body on the i^{th} day by inhalation or via a contaminated wound.

The bioassay data are denoted by y_j for $j = 1$ to M, with uncertainty estimates (standard deviations) σ_j. The number of possible intakes N exceeds the number of data points M, usually by a large factor.

The biokinetic response is assumed to be one of a known finite set of linear functions (the biokinetic response in this case is the fraction of intake excreted

in urine as a function of time) of the form

$$f_j^{(l)} = \sum_i x_i u_{ij}^{(l)}, \tag{1}$$

where l denotes a particular intake type. Equation 1 gives the predicted bioassay result at time j given intakes x_i, where $u_{ij}^{(l)}$ is the l^{th} biokinetic response function at time j for unit intake at time i.

The bioassay data uncertainty σ_j is in fact a function of the predicted bioassay result $f_j^{(l)}$. For example, part of the uncertainty may come from biological variability of the urine excretion process, which is proportional to how much is being excreted.

Our desire is to determine the "best fit" values of $\{x_i\}$ and l given $\{y_j\}$ (read $\{x_i\}$ as "the set of x_i for all i"). The method described here is to define "best fit" as the expectation value of the Bayesian posterior probability distribution, given the data and a prior probability distribution (for a good reference on Bayesian methods see Ref. [1]).

The prior probability distribution of $\{x_i\}$ and l is denoted by $P(\{x_i\}, l)$. We assume that the prior probability of l is independent of time and that intakes occuring at different times are independent and have an equal probability of occurrence, so that

$$P(\{x_i\}, l) = P(l) \prod_i P(x_i|l), \tag{2}$$

where $\prod$ denotes the product. The quantity $P(x_i|l)$ is the conditional probability of x_i given intake type l (the vertical bar is read as "given"). Since it represents the probability density function of a continuous variable x_i, it needs to be multiplied by dx_i to obtain the probability that x_i is in interval dx_i (this is our notational convention for continuous variables). Also, $P(l)$ represents the prior probability of intake type l. It is convenient to define the conditional prior probability measure $W\,dX$ as

$$W\,dX \equiv \prod_i P(x_i|l) dx_i. \tag{3}$$

Assuming independent Gaussian measurement uncertainties, the probability distribution of measurements $\{y_j\}$ given intakes $\{x_i\}$ and intake type l, often referred to as the likelihood function, is given by

$$\begin{aligned} P(\{y_j\}|\{x_i\}, l) &= \prod_j \frac{1}{\sqrt{2\pi}\sigma_j} \exp\left[-\frac{(y_j - f_j^{(l)})^2}{2\sigma_j^2}\right] \\ &= C\,F, \end{aligned} \tag{4}$$

where C is a constant (independent of $\{x_i\}$ and l) and

$$F = \left(\prod_j \frac{1}{\sigma_j}\right) \exp\left(-\frac{\chi^2}{2}\right), \tag{5}$$

with

$$\chi^2 = \sum_j \frac{(y_j - f_j^{(l)})^2}{\sigma_j^2}. \tag{6}$$

From Bayes' theorem, the posterior probability distribution of intakes $\{x_i\}$ and intake type l given data $\{y_j\}$, is given by

$$\begin{aligned} P(\{x_i\}, l|\{y_j\}) &\propto P(\{y_j\}|\{x_i\}, l)P(\{x_i\}, l) \\ &\propto P(l)FW\, dX. \end{aligned} \tag{7}$$

For any function g of $\{x_i\}$ and l, the expected value of g over the Bayesian posterior distribution is therefore

$$E(g) = \frac{\sum_l P(l) \int gFW\, dX}{\sum_l P(l) \int FW\, dX}. \tag{8}$$

3 Scaling With the Intake Time Interval

Let the total time interval for possible intakes be denoted by T. The time interval T has been divided into N equal subintervals of size $\Delta t \equiv T/N$, where intakes x_i may have occurred, for $i = 1, N$. The time scale for specifying intakes depends on the biokinetic response (the urine excretion pattern following an intake of unit amount). Intakes need to be specified on the time scale of the most rapid biokinetic response; however, since urine collection is a discrete process that is reasonably averaged over a day, Δt is often taken as one day.

From a mathematical standpoint it is interesting to imagine that urine excretion is a continuous process, and consider the limit $\Delta t \to 0$. In this limit, the prior probability of an intake with amount in the range dx_i occurring in the i^{th} time interval Δt, is

$$w(x_i)\Delta t dx_i, \tag{9}$$

for $x_i > 0$, where $w(x_i)$ is a positive function giving the intake probability per unit time (for notational simplicity the dependence of w on intake type l has not been explicitly shown). The important scaling relation is that the intake probability approaches zero as the time interval goes to zero. This means that the normalized prior probability distribution function is of the form

$$W\, dX = \prod_{i=1}^{N} \left\{ [\delta(x_i)(1 - \lambda\Delta t) + w(x_i)\Delta t]\, dx_i \right\}, \tag{10}$$

where the delta function $\delta(x_i)$ represents the probability of no intake in the time interval Δt (the delta function can be thought of as the limit of functions that are nonzero only in a small region around 0 and such that $\int \delta(t)dt = 1$, as the size of the region approaches zero) and

$$\lambda = \int_0^\infty w(x_i)dx_i. \tag{11}$$

Equation 10 can be interpreted as a product of mixture distributions in which, for the i^{th} time interval of length Δt, there either is no intake of any positive amount x_i with probability $1 - \lambda\Delta t$ or there is an intake of positive amount x_i having conditional probability $w(x_i)\,dx_i/\lambda$ with probability $\lambda\Delta t$. Also, Δt is assumed to be sufficiently small such that the probability of two or more intakes in Δt (of order Δt^2) can be ignored. The probability is correctly normalized because

$$\int_0^\infty [\delta(x_i)(1 - \lambda\Delta t) + w(x_i)\Delta t]\, dx_i = 1. \tag{12}$$

4 Poisson Sum Representation

Equation 10 can be algebraically reduced to a sum of terms representing different numbers of intakes. The first three terms representing 0, 1, and 2 intakes are as follows:

$$\begin{aligned}
\text{no intakes} \quad &: \quad (1 - \lambda\Delta t)^N \prod_{i=1}^{N} \delta(x_i)dx_i \\
\text{1 intake} \quad &: \quad (1 - \lambda\Delta t)^{N-1}\ N\lambda\Delta t\ \frac{1}{N}\sum_i \Big[\frac{w(x_i)}{\lambda}dx_i \prod_{\substack{i'=1 \\ i'\neq i}}^{N} \delta(x_{i'})dx_{i'}\Big] \\
\text{2 intakes} \quad &: \quad (1 - \lambda\Delta t)^{N-2}\ \frac{N(N-1)}{2}(\lambda\Delta t)^2 \\
&\times \quad \frac{1}{N}\sum_i \Big\{ \frac{w(x_i)}{\lambda}dx_i \frac{1}{N-1}\sum_{\substack{i'=1 \\ i'\neq i}}^{N} \Big[\frac{w(x_{i'})}{\lambda}dx_{i'} \prod_{\substack{i''=1 \\ i''\neq(i,i')}}^{N} \delta(x_{i''})dx_{i''}\Big]\Big\}
\end{aligned} \tag{13}$$

In the term representing 2 intakes, the factor $N(N-1)/2$ has the 2 in the denominator because of the 2! (2 factorial) different possible orderings of the 2 time intervals i and i'.

By inspection of Eq. 13, the general binomial term representing n intakes has the coefficient

$$P_n = (1 - \lambda\Delta t)^{N-n}\binom{N}{n}(\lambda\Delta t)^n. \tag{14}$$

Now, approximating for $n << N$ (i. e., the number of intakes is much smaller than the number of time intervals where intakes could occur),

$$\binom{N}{n} = \frac{N!}{n!(N-n)!} \approx \frac{N^n}{n!}, \tag{15}$$

$$(1 - \lambda\Delta t)^{N-n} = (1 - \lambda\frac{T}{N})^{N-n} \approx (1 - \lambda\frac{T}{N})^N \approx e^{-\lambda T}, \tag{16}$$

and therefore,

$$P_n \approx e^{-\lambda T} \frac{(\lambda T)^n}{n!}, n = 0, 1, \ldots, \tag{17}$$

the Poisson probability for n events, when the average number of events is λT.

One may also recognize Eq. 14 as the binomial distribution of n successes in N independent Bernoulli trials with probabilities $p = \lambda \Delta t$ for success and $q = 1 - p$ for failure. The Poisson approximation holds if N is sufficiently large and p is small.

The Poisson probability is normalized, so that

$$\sum_{n=0}^{\infty} P_n = 1. \tag{18}$$

The sums over time intervals in Eq. 13 will convert to integrations over continuous time using the replacement

$$\frac{1}{N} \sum_i \rightarrow \frac{1}{T} \int dt. \tag{19}$$

In term-by-term integration over Eq. 13, the δ functions disappear. It is convenient to define a prior probability measure for n intakes as

$$W_n \, dX_n \equiv \overbrace{\frac{dt}{T} \frac{w(x_t)}{\lambda} dx_t \ldots \frac{dt'}{T} \frac{w(x_{t'})}{\lambda} dx_{t'}}^{\text{product of } n \text{ terms}} \tag{20}$$

This probability measure is normalized, so that

$$\int W_n \, dX_n = 1. \tag{21}$$

The Poisson sum representation of Bayesian posterior expectations, corresponding to Eq. 8, is given in terms of $W_n \, dX_n$ as

$$E(g) \equiv \frac{\sum_{n=0}^{\infty} P_n \sum_l P(l) \int g F W_n \, dX_n}{\sum_{n=0}^{\infty} P_n \sum_l P(l) \int F W_n \, dX_n}. \tag{22}$$

Equation 22 can also be written as

$$E(g) = \sum_{n=0}^{\infty} E(g|n) m(n), \tag{23}$$

in terms of the conditional expectation of g given n intakes defined by

$$E(g|n) \equiv \frac{\sum_l P(l) \int g F W_n \, dX_n}{\sum_l P(l) \int F W_n \, dX_n}, \tag{24}$$

and the marginal probability of n intakes, defined by,

$$m(n) \equiv \frac{P_n \sum_l P(l) \int F W_n \, dX_n}{\sum_{n=0}^{\infty} P_n \sum_l P(l) \int F W_n \, dX_n}. \tag{25}$$

5 The Unfolding Algorithm

In what follows a simplified algorithm that avoids the multiple integrations of Eq. 22 is discussed. It is assumed that the time interval between bioassay samples is small enough that the probabilities of two or more intakes is negligibly small. This requires the average number of intakes from the prior probability distribution, $\lambda\Delta t$, to be small. In other words, in the sampling interval Δt there are 0 or 1 intakes with probabilities P_0 and P_1 given by

$$\begin{aligned} P_0 &= \exp(-\lambda\Delta t), \\ P_1 &= 1-\exp(-\lambda\Delta t) \end{aligned} \tag{26}$$

(We choose this form rather than $P_0 = 1-\lambda\Delta t$, $P_1 = \lambda\Delta t$ to more easily handle cases where $\lambda\Delta t$ is somewhat large).

Equation 22 is applied to the i^{th} sampling interval in the following way. Consider a function $g(x_i, l)$ of the intake amount x_i and intake type l. Firstly the integration over time in Eq. 19 is replaced by evaluation at the central time of the interval. The expected value of g is then given by

$$E(g) = \frac{P_0 g(0) + P_1 \sum_l P(l) \int \frac{w(x_i)}{\lambda} \frac{F(x_i)}{F(0)} g(x_i)\, dx_i}{P_0 + P_1 \sum_l P(l) \int \frac{w(x_i)}{\lambda} \frac{F(x_i)}{F(0)}\, dx_i}, \tag{27}$$

where $w(x_i)$ is the prior probability distribution of the intake amount x_i (a log-normal form is assumed), and $F(x_i)/F(0)$ is the ratio of likelihood functions given by

$$\frac{F(x_i)}{F(0)} = \left[\prod_j \frac{\sigma_j(0)}{\sigma_j(x_i)}\right] \exp\left(-\frac{\chi^2(x_i, l) - \chi^2(0)}{2}\right), \tag{28}$$

where j enumerates the data points used to determine the intake if more than the righthand data point of the interval is used. In Eq. 27 we have used the fact that there is no dependence on intake type l when there is no intake, and

$$\sum_l P(l) = 1. \tag{29}$$

It is sometimes convenient to rewrite Eq. 27 in the form

$$E(g) = \sum_l E(g|l, y) P(l|y), \tag{30}$$

where $E(g|l, y)$, the posterior expectation value of g given l and the data, is given by

$$E(g|l, y) = \frac{P_0 g(0) + P_1 \int \frac{w(x_i)}{\lambda} \frac{F(x_i)}{F(0)} g(x_i)\, dx_i}{P_0 + P_1 \int \frac{w(x_i)}{\lambda} \frac{F(x_i)}{F(0)}\, dx_i}, \tag{31}$$

and $P(l|y)$, the posterior probability of intake type l given the data, is given by

$$P(l|y) = \frac{P_0 + P_1 \int \frac{w(x_i)}{\lambda} \frac{F(x_i)}{F(0)}\, dx_i}{P_0 + P_1 \sum_l P(l) \int \frac{w(x_i)}{\lambda} \frac{F(x_i)}{F(0)}\, dx_i} P(l). \tag{32}$$

The variance of a an arbitrary function $g(x_i, l)$ can always be calculated in terms of expectation values thus:

$$\mathrm{Var}(g) = E(g^2) - E(g)^2. \tag{33}$$

In the evaluation of $\chi^2(x_i, l)$, defined by Eq. 6 (although now we make the dependence on x_i and l explicit), the calculated urine excretion at the time of the j^{th} data point is given by

$$f_j^{(l)} = x_i u_{ij}^{(l)} + \sum_{i'<i} x_{i'} u_{i'j}^{(l)}, \tag{34}$$

rewriting Eq. 1 to show how it depends on the intake x_i and previous intakes. The summation above extends over all previously determined intakes $x_{i'}$ that have occured earlier in time. The uncertainty variance of the j^{th} data point $\sigma_j^2(x_i)$, which enters into $\chi^2(x_i, l)$, contains four components:

$$\sigma_j^2(x_i) = \sigma_{mj}^2 + (B_v f_j)^2 + (B_v x_i u_{ij})^2 + \sigma_j'^2, \tag{35}$$

measurement uncertainty, sample collection/biological variability equal to the coefficient of variation B_v times the Bayesian posterior expectation excretion f_j coming from earlier intakes at the time of the j^{th} sample, sample collection/biological variability associated with the new intake, and uncertainty of the calculated excretion due to earlier intakes. The latter is given by

$$\sigma_j'^2 = \sum_{i'<i} \mathrm{Var}(x_{i'} u_{i'j}^{(l)}). \tag{36}$$

The variances add since the earlier intakes are determined by separate blocks of data and are statistically independent. In calculating variances of an arbitrary quantity d proportional with coefficient D_l for intake type l to an intake amount x_i as in Eq. 36, we use the formulas

$$\begin{aligned} E(d) &= \sum_l D_l E(x_i|l, y) P(l|y) \\ \mathrm{Var}(d) &= \sum_l D_l^2 E(x_i^2|l, y) P(l|y) - E(d)^2. \end{aligned} \tag{37}$$

For a discussion of sample collection/biological variability see Ref. [18]. For true 24 hour samples we use $B_v = 0.1$; for specific-gravity corrected, simulated 24 hour samples, we use $B_v = 0.3$.

A subtlety caused by having the uncertainty depend on x_i is that for data values that are many standard deviations negative (normally very rare), the Bayesian posterior mean tends to be large and positive. In other words, large negative data is explained as statistical variation from a large positive true value allowed by large sample collection/biological variability uncertainty. In practice, problems are avoided by 1) by increasing the measurement error uncertainty of negative data values so they are no more than some given number (say 2) of standard deviations negative and 2) by increasing the propagated uncertainty of excretion from earlier intakes so that data minus background satisfies the same criterion.

Data unfolding depends on causality, that excretion follows intake in time, so that intakes in a given sampling interval affect only subsequent urine excretion amounts and not urine excretion amounts preceding the intake. Thus, starting with the first (earliest in time) sampling interval, the intake in each sampling interval is determined by the right-hand urine data value of that interval, as the expectation value of the Bayesian posterior probability distribution, using Eq. 27 with $g(x_i) = x_i$. For all intervals except the first, the excretion expected from previous intakes and its propagated uncertainty is included in this calculation because of Eq. 35.

Unfolding then becomes a sequence of one-dimensional integrals over intake amounts using Eq. 27 to determine expectation values and variances from the posterior distribution. Figure 1 shows the result of unfolding bioassay data in this manner. This example uses numerically generated data, for a low level tritium case (the biokinetic response is assumed to be a simple exponential with a 10 day half life). Figure 2 shows the result of the first step of the iterative unfolding process, where 9 intake amounts are determined as expectation values using Eq. 27 with χ^2 determined by one data point (the right-hand data point) in each of the 9 sampling intervals.

After carrying out the first data unfolding as described, we obtain a set of intake amounts x_i for each bioassay sampling interval, and we can calculate the Bayesian posterior probability for each intake as the marginal probability of an intake given by Eq. 25. In this situation, the intake probability is equivalently calculated using Eq. 27 with $g(x_i, l) = 1$ for $x_i > 0$.

A single step in the iterative process consists of dropping the least probable intake and repeating the unfolding. The iteration is stopped when the minimum of all the intake probabilities exceeds some limit (say 0.5). The exact value of the intake probability limit is not very critical, since intakes tend to have either very small probabilities or probabilities near 1.

For the example shown in Fig. 1, the intake in the first sampling interval was the least probable after the first iteration, so it was dropped in the second iteration. The second iteration repeated the unfolding, assuming no intake was possible in the first sampling interval. In this case all the expectation integrals (starting with the second subinterval) needed to be recalculated, since the excretion tail produced by the first intake is no longer present in the later

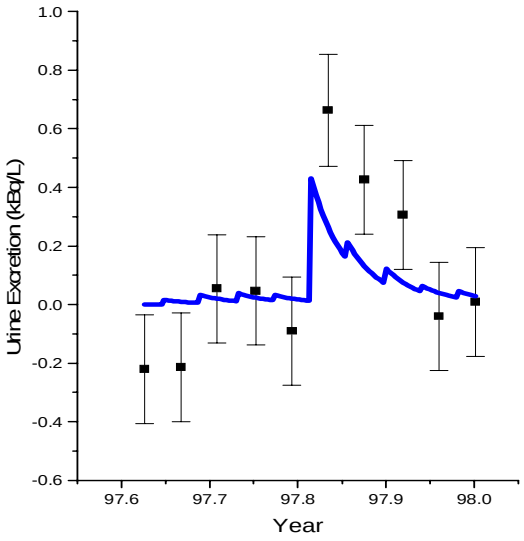

Figure 1: Urine bioassay data and a calculation result based on data using the Bayesian posterior expected values of intakes in each monitoring interval.

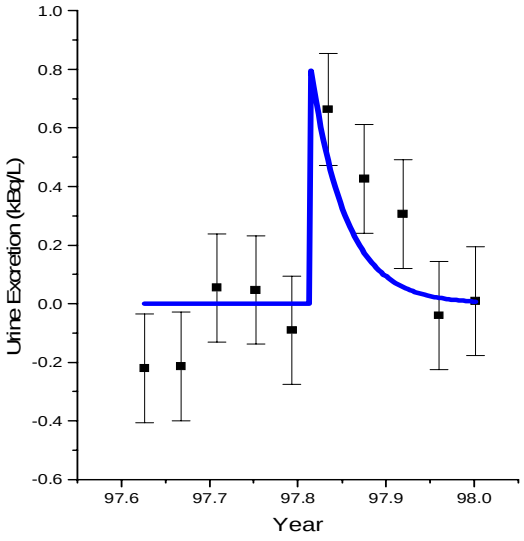

Figure 2: Final expected urine excretion curve.

subintervals. If, say, the intake in the 6th subinterval rather than the 1st had the smallest probability and was dropped, then the 6th and 7th data points would have been used to redetermine the intake in the subinterval between the 5th and 6th data points, and all subintervals to the right would have needed to be recalculated. The algorithm proceeds in this way, using separate blocks of data to determine single intakes, iterating the unfolding process until all the remaining intakes have probabilities exceeding the prescribed limit. The final result for the example shown in Fig. 1 is shown in Fig. 2. In this case only one highly probable intake remains, with Bayesian posterior probability of 0.97, reproducing the intake assumed to generate the data.

This method results in an intake scenario with relatively few, well determined, intakes, well suited to the reality of most occupation monitoring situations, where intakes are rare, and to the regulatory requirement that all intakes be reported and justifiable (see Code of Federal Regulations 10CFR835).[2] An intake scenario with relatively few intakes results in higher dose estimates for cases with nonzero dose, as has been discussed (see Miller and Inkret, 1996).[16]

In contrast, simple unfolding techniques are not probabilistic. The intake in each sampling interval is determined so that calculated excretion matches the right-hand urine excretion data value exactly, even if the required intake amount is negative. Also there is no method to calculate uncertainties in the excretion expected from intakes occurring at earlier times, which is an important background that must be subtracted to determine if new intakes have occurred. Finally, there is no way to determine intake probability, in order, say, to drop improbable intakes.

A final consistency check is to see whether the calculated excretion is statistically consistent with the observed excretion. A measure of statistical consistency is the overall χ^2 given by

$$\chi^2 = \sum_j \frac{(y_j - j_j)^2}{\sigma_j^2}, \tag{38}$$

where f_j is the Bayesian posterior expectation value of excretion from all intakes at the time of the j^{th} data point. In this case, σ_j^2 is calculated as

$$\sigma_j^2 = \sigma_{mj}^2 + (B_v f_j)^2 \tag{39}$$

in terms of measurement uncertainty and sample collection/biological variability uncertainty. Roughly, χ^2/M should be about 1, where M is the number of data points, for the final result to be statistically consistent. Cases with larger values of χ^2/M are, regardless of the exact normalization, more questionable.

An example of an actual ^{238}Pu case is shown in Fig. 3. This example is discussed in detail in Appendix B. In this case there are three calculated intakes, two of which are not associated with known incidents. The cumulative committed dose is 0.14 Sv $\times\div$ 1.8; χ^2/M is 1.5 for $M = 37$ data points. The use of a multiplicative factor to express uncertainty is discussed in Appendix C.

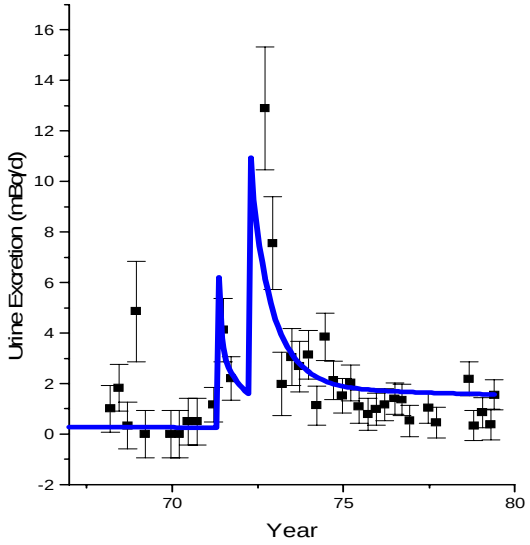

Figure 3: Actual ^{238}Pu case having 3 calculated intakes.

6 Discussion

A simple use of the Poisson sum formalism is the unfolding algorithm. This has been implemented in the UF (unfolding) code. The quantities λ and the log-normal parameters are prescribed functions of time, describing how the prior distribution varies with time. Ideally, these functions are determined iteratively, by assuming some reasonable initial values, calculating intakes for a population of workers, and then determining population averages of the distribution of intakes for different historical periods, to be used to determine the new prior distribution. This iteration process is continued until it converges.

For non-routine situations (accidents or other off normal occurrences), where there is information from workplace indicators (for example, nasal swipes or air monitor levels) that an intake may have occurred , then the time of the possible intake is known and its prior probability is specified as a discrete probability that an intake occurred based on values of the workplace indicators. For example, this probability might be taken to be 0.5 for the usual range of workplace indicators and might even be 1 in extreme cases. The prior probability parameters (the parameters of the log normal distribution) are discretely specified for a non-routine intake. The prior probability distribution for a known occurrence can be used to incorporate the results of other measurements, for example, *in vivo* lung counts. In an accident situation where good lung data is available, in analyzing the urine data the prior probability of an intake would be set to 1,

and the prior probability distribution parameters would reflect the lung count measurement results and associated uncertainties.

One of the advantages of the present formalism is that it mathematically describes the intuitive concept of the number of intakes, being able to address questions such as whether or not an intake has occurred, since these are concepts often used in practice.

The UF code has been used to analyze plutonium urinalysis data for everyone in the Los Alamos database (some 14000 people–requiring about 30 hours on a Pentium workstation), giving encouraging results. A trial software and documentation package for the UF code is available for download from our Bayesian World Wide Web site http:\\www.lanl.gov\Bayesian (Bayesian software package II).

An entropy form of the prior probability distribution for daily radionuclide intake was investigated previously (Miller and Inkret, 1996)[16]. This form of the prior probability distribution was not able to model the infrequent acute intake scenarios that are often observed in practice. In particular, the standard deviation divided by the mean of the entropy distribution is fixed, unlike the prior probability distributions considered in this paper. To see this property of distributions with a δ function component (representing "no intake"), let $w(x)/\lambda$ be a probability distribution with mean μ and standard deviation σ. The distribution

$$\delta(x)(1-p) + p\frac{w(x)}{\lambda} \tag{40}$$

then has standard deviation divided by mean given by

$$\frac{\sqrt{\sigma^2 + \mu^2(1-p)}}{\mu} \; \frac{1}{\sqrt{p}}, \tag{41}$$

which becomes arbitrarily large as $p \to 0$.

The most ambitious application of the Poisson sum formalism is to the entire time interval over which urine data have been collected and not sampling interval by sampling interval using data unfolding. As we have shown, a solution of the internal dosimetry problem can be written down quite elegantly and concisely in terms of Bayesian posterior expectation values. This would seem to be the definitive solution of the problem, provided the calculations can be carried out. In plutonium internal dosimetry, the number of possible intake days, N, is quite large, often of order 10000. In this situation, direct evaluation of the 10000-dimensional integral given by Eq. 8 is out of the question. Often, however, the average number of intakes in a population is small. In this case, the Poisson sum representation converges rapidly for small numbers of intakes. Evaluation of the requisite low dimensional integrals appearing in Eq. 22 is then feasible, say, using Markov Chain Monte Carlo methods (Tierney, 1994, Gilks et. al., 1996)[25][6]. We have made some initial explorations of this technique with encouraging results.

7 Acknowledgments

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A Appendix–Biokinetic models

Any set of biokinetic response functions may be used with these methods, obtained by varying parameters of a preferred biokinetic model. The choice of finite, discrete set of biokinetic response functions to span what is actually a multi-dimensional space is an approximation that has some effect on the calculated results and uncertainties. This is an area of Bayesian "subjectivity" that relies on professional judgment. To illustrate in more detail the use of biokinetic models, we will discuss the case of plutonium in detail in this appendix.

For plutonium internal dosimetry, we use biokinetic response functions based on the ICRP publication 30[10] model, since this is currently the basis of U. S. Department of Energy regulations.

A computer code has been developed to calculate the ICRP publication 30 model and generate the required tables of linear biokinetic response functions. These tables are included in the Bayesian software package II that may be downloaded from our web site http:\\www.lanl.gov\Bayesian.

In principle, the code CINDY[23] might be used to calculate biokinetic response functions; however, there is no provision for writing files of a specified format, and also we found it necessary to go outside of the ICRP publication 30 framework and introduce time-varying solubility time constants in order to describe the observed behavior of certain cases involving Pu-238, which will be discussed later. Where possible, we have checked our results against CINDY and have found them to be in agreement.

The plutonium biokinetic model consists of some 30 coupled linear first-order differential equations in time that have widely disparate time scales, from 0.01 day to 10000 days. Thus, the simplest explicit methods of solving differential equations are not adequate. However, the solution of these equations with the Gear method[5] subroutine LSODE[9] does not present any particular problem.

A.1 Standard Plutonium Biokinetic Models

The compartmental biokinetic model for plutonium is shown schematically in Fig. 4.

The urine excretion model is based on the Langham injection studies[12]. In calculating urine excretion, the intake to the blood compartment from the lung and small intestine is treated as an equivalent rate of injection. The four-component exponential Jones fit (J1 through J4)[11] is used to represent the

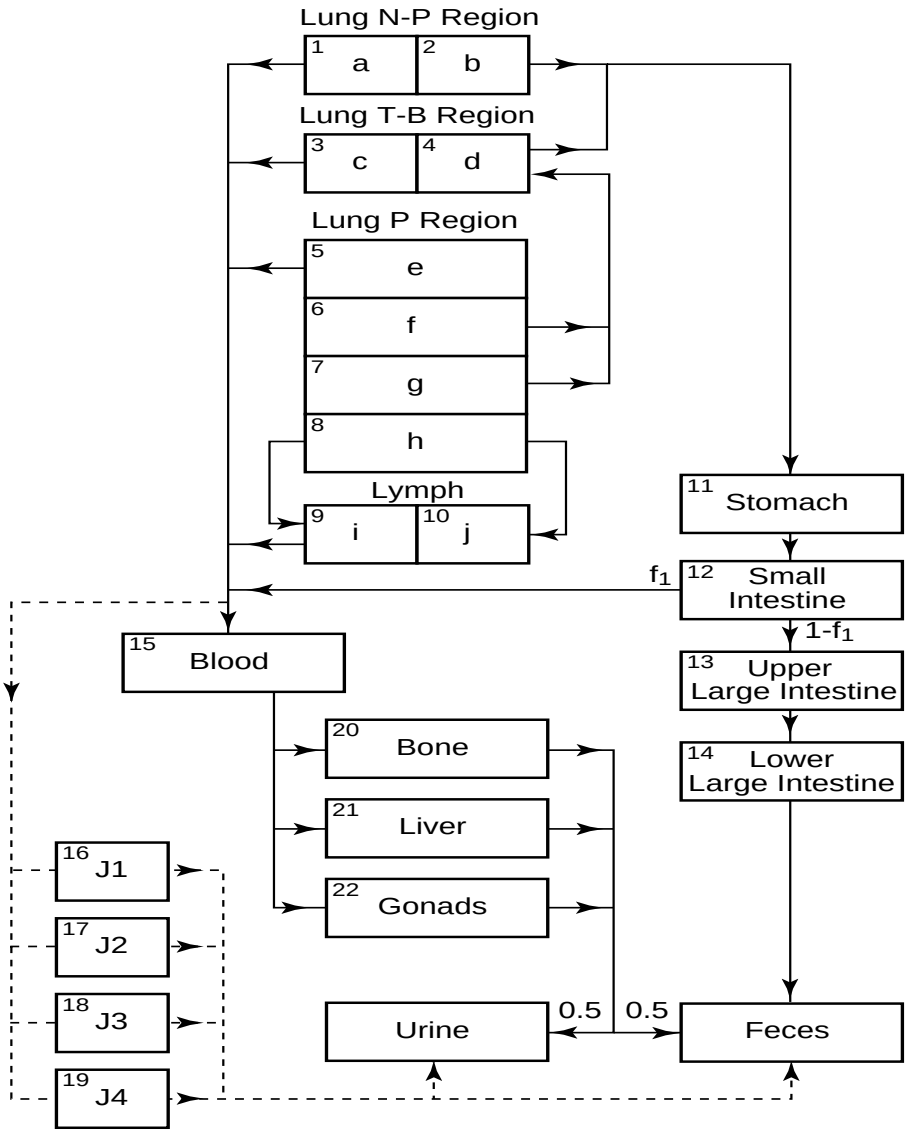

Figure 4: Biokinetic model for plutonium.

data from the injection studies.

The existence of the injection studies data is extremely important for plutonium internal dosimetry. Any biokinetic model must then agree with this data in reproducing injection/urine-excretion behavior. Thus any biokinetic model that reproduces the urine excretion pattern must have the same equivalent injection into the blood, in the case of inhalation, coming from the lungs. Given this constraint, it is unlikely if not impossible for different plutonium biokinetic models to disagree by a large factor in dose predicted from urine excretion.

The calculations are carried out using the FORTRAN 77 program BIOK, which relies on the subroutine LSODE[9] to solve the differential equations.

Doses are calculated as a function of time by the program BIOK for the following organs: lung, bone surface, bone marrow, liver, and gonads. Following ICRP publication 30[10], plutonium is assumed to reside on bone surfaces. Under these assumptions, the single bone compartment actually consists of two equal subcompartments, trabecular and cortical bone. The specific effective energy (SEE) matrix is diagonal, except for these bone components as shown in Table 1.

Table 1: SEE matrix components for bone (MeV per transformation of ^{239}Pu).

target	cort bone	trab bone
r. marrow		0.034
bone surf	0.21	0.21

Thus, the dose to the red marrow is a constant factor $0.034/(0.21 + 0.21) = 0.08$ times the bone surface dose.

The gonadal dose for a woman, to ovaries rather than testes, is a constant factor 0.314 times that for a man, corresponding to the ratio of assumed fractional amounts transferred from the blood.

The output from BIOK consists of a table of urine excretion and doses (effective whole body and individual organ) as functions of time, which is meant to summarize, by interpolation, the entire excretion and dose pattern. Such tables are calculated for a set of standard intake models denoted by a three character code, for example, *iym* denoting inhalation of class Y medium (1 μm AMAD) particle size. Results are also calculated for small (for example *iys*, 0.2 μm AMAD) and large (for example *iyl*, 5.0 μm AMAD) particle sizes, and for class W.

Wounds are simulated by using the compartment structure of the lung model but changing parameter values. By setting the fractional depositions $f_a = f_c = 1$ in the two upper lung regions, effectively making the lung consist of only the two compartments a and c, these lung compartments are used to simulate two wound compartments. Three wound models have been defined with intake codes *wnd*, *wdt*, and *win*. The parameters for *wnd* are obtained from the

observed movement of plutonium out of soft tissues for six human cases[4], where it is seen that 1/3 has a retention half time of about 7 days, and 2/3 has a retention half time of about 500 days. The parameter values for *wdt* are based on fitting data from a particular Los Alamos case. The parameters for *win* correspond to prompt, complete injection of material from the wound to the bloodstream. Values of the deposition fractions and time constants for the a and c lung compartments for the three wound models are shown in Table 2. In Table 2, D_{NP} and D_{TB} are the deposition fractions in the Nasal Passage

Table 2: Lung model parameters used to simulate wound compartments.

intake code	D_{NP}	D_{TB}	T_A(d)	T_C(d)
wnd	0.67	0.33	500	7
wdt	0.7	0.3	30	1
win	1.0	0.0	0.1	

(NP) and Trachea and Bronchial tree (TB) regions of the lung, and T_A and T_C are retention half times of compartments a and c.

A.2 Special ^{238}Pu model based on Wing 9 Accident

In 1971 an accident occurred in wing 9 of the CMR building at Los Alamos involving inhalation of plutonium 238, where the observed urine excretion from a number of highly exposed individuals showed an unexpected behavior. There was little excretion of plutonium for a time on the order of 100 days, and then the excretion rate rose to large values. This type of behavior disagrees with the standard models, class Y or W and different particle sizes. Guilmette and Hickman et. al.[7][8] adapt a biokinetic model developed for canine studies to describe this behavior. The published paper contains an error of a factor of 10 in the calculated doses (the published doses are too small).[15] We sought to describe the behavior within the framework of the ICRP publication 30 model to be consistent with the other models we use.

The ICRP publication 30 model was modified as follows. The lung compartments a, c, e, and i, which feed the blood, are assumed to have time varying solubility time constants, initially very long, corresponding to highly insoluble material, and then changing to normal values for class Y material, with the change of time constants taking place over some time τ. Following work at Hanford, which defined class super-Y plutonium, the initial insoluble time constant is taken as 10000 d [24]. Therefore, the a, c, e, and i, compartment half times are assumed to be themselves functions of time. We arbitrarily choose the simple analytical form

$$\tau_a = \frac{\tau_{aI} + \tau_{aY}\frac{t}{\tau}}{1 + \frac{t}{\tau}}, \tag{42}$$

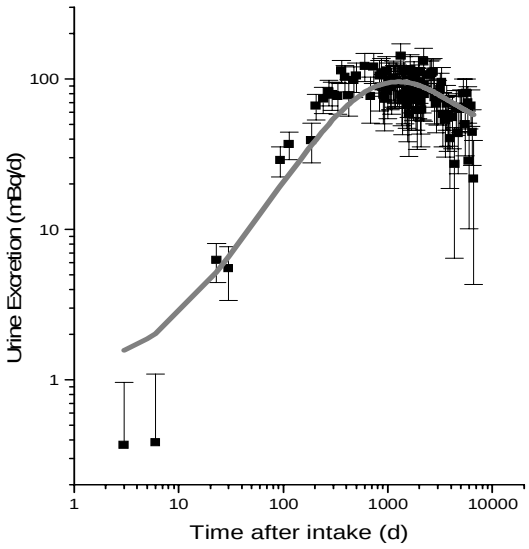

Figure 5: Urinalysis data from an individual involved in Wing 9 incident and fit, showing the slow onset of plutonium excretion.

where τ_a is the half time of compartment a, τ_{aI} is the initial insoluble half time of 10000 days, τ_{aY} is the normal class Y half time, and τ is a parameter specifying the time scale of this change of solubility process. The parameter τ, and the particle size, were adjusted to best fit data from a particular case shown in Fig. 5. Using autoradiography of dog lung tissue samples, Mewhinney and Diel[14][3] have identified the underlying physical process causing the change of solubility as fragmentation of larger insoluble particles by α activity.

The quantity τ was found to have the optimum value $\tau = 7$ days and the particle size AMAD $= 0.2\mu$m. The fit obtained from this case (denoted by the three-character code *iee*) was found to adequately fit the other wing 9 cases as well, as shown in Table 3. Table 3 gives the intake amounts, committed effective dose equivalent (CEDE), corrected CEDE from Ref. [8], and values of χ^2/M, for the seven wing-9 cases with the largest intakes. For a fit to be statistically acceptable, χ^2/M should be on the order of 1, as is seen to be the case. Our time-varying solubility ^{238}Pu model is seen to give CEDE's that are about a factor of 1.5 larger than those from Ref. [8].

Table 3: χ^2/M for the wing 9 cases with the largest intakes.

intake(kBq)	CEDE(Sv)	CEDE(Sv) Ref. [8]	χ^2/M	M
79	12.30	8.4	0.85	80
59	9.10	5.9	1.12	96
43	6.60		2.0	5
43	6.60	4.2	0.8	71
14.1	2.20	1.4	1.4	62
8.1	1.25	0.84	1.2	64
7.8	1.20	0.80	1.1	47

B Appendix–Example using real ^{238}Pu data

In this appendix an example using real ^{238}Pu data is discussed in detail. The urine bioassay data are given in table 4 and displayed in Fig. 6 (this data is also downloadable from our web site http:\\www.lanl.gov\Bayesian, Bayesian software package II, file *urine.ex*). This example was selected because it had multiple intakes and relatively few urine data points.

The subject worked with plutonium since the mid 1940's, was involved in several ^{239}Pu incidents in the 1940's, and had several ^{239}Pu intakes. The subject's ^{238}Pu urine bioassay record begins in 1968, when specific analysis for ^{238}Pu started at Los Alamos.

The same urine collection protocol was used for all samples, and the biological/sample collection variability is assumed to be 30% of the true amount present. The limiting probability for an intake is assumed to be 50%, that is, lower probability intakes are dropped. The form of the prior probability distribution of intake amount x is assumed to be delta function plus log normal, with the log normal having the form

$$P(x) = \frac{1}{\sqrt{2\pi}\sigma_g x} \exp\left[\frac{-(\log\frac{x}{x_1})^2}{2\sigma_g^2}\right], \tag{43}$$

where $\sigma_g = 2$ and $x_1 = 37\,\mathrm{Bq}$. The prior probability of an intake in the time range of this data was assumed to be 5% per year before 1/1/1970 and 1% per year after. As a result of the incidents in the 1940's (early ^{239}Pu mixtures used at Los Alamos nominally contained about 10% ^{238}Pu by activity), a discrete prior probability of 25% for an intake on 6/9/1945 was assumed. For this discrete incident-related prior, the quantity x_1 in Eq. 43 above was 370 Bq.

Under these assumptions the unfolding algorithm gave the results shown in Table 5 with the average calculated urine excretion displayed in Fig. 3 (the calculations may be done using the unfolding program downloadable from our web site, by copying the file *urine.ex* into the urine input file *urine.in* and exe-

Table 4: Pu-238 Urinalysis Results

Collected date(MM/DD/YYYY)	Excretion(mBq/d) ± 1 SD
03/15/1968	1. ± 0.9
06/13/1968	1.8 ± 0.9
09/13/1968	0.3 ± 0.9
12/13/1968	4.8 ± 2.
03/20/1969	0. ± 0.9
12/18/1969	0. ± 0.9
03/19/1970	0. ± 0.9
06/18/1970	0.5 ± 0.9
09/24/1970	0.5 ± 0.9
03/18/1971	1.2 ± 0.7
06/29/1971	4.1 ± 0.7
09/22/1971	2.2 ± 0.5
09/18/1972	12.9 ± 1.6
12/08/1972	7.5 ± 1.1
03/15/1973	2. ± 0.4
06/27/1973	3. ± 0.6
09/17/1973	2.7 ± 0.5
12/21/1973	3.1 ± 0.6
03/21/1974	1.1 ± 0.4
06/17/1974	3.8 ± 0.7
09/16/1974	2.1 ± 0.5
12/18/1974	1.5 ± 0.4
03/17/1975	2. ± 0.4
06/16/1975	1.1 ± 0.4
09/19/1975	0.8 ± 0.4
12/17/1975	1. ± 0.4
03/17/1976	1.2 ± 0.4
07/02/1976	1.4 ± 0.4
09/12/1976	1.4 ± 0.4
12/08/1976	0.5 ± 0.4
06/24/1977	1. ± 0.4
09/15/1977	0.4 ± 0.4
09/01/1978	2.2 ± 0.5
10/20/1978	0.3 ± 0.4
01/18/1979	0.9 ± 0.4
04/20/1979	0.4 ± 0.4
05/28/1979	1.6 ± 0.4

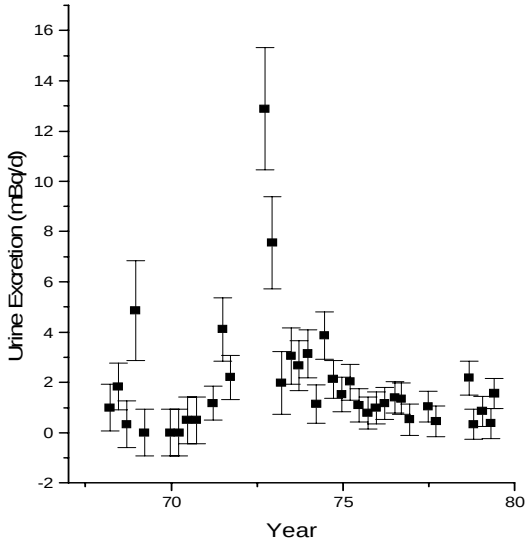

Figure 6: Actual ^{238}Pu urine data.

cuting *uf.exe* following the instructions in the file *readme.1st* and the instruction manual *manual.pdf*).

Table 5 shows for the calculated intakes (most of this information comes from the output file *ufint.dat* described in the documentation): 1) the number of urine data points M in the data block used to determine the intake, 2) the Bayesian posterior probability of the intake (must be larger than the limiting probability of 50 %), 3) the intake type l denoted by a three-character code defining a biokinetic model discussed in Appendix A, the Bayesian posterior expectation value of χ^2/M for intake type l, the Bayesian posterior probability $P(l|y)$ of intake type l given the data, 4) the Bayesian posterior probability of an intake $P(\text{intake}|l, y)$ given model l and data (which can be calculated as $E(g|l, y)$ using Eq. 31 for the particular value of l, where $g(x_i, l) = 1$ for $x_i > 0$, otherwise 0), 5) the Bayesian posterior expectation value of the intake amount x in units of 37 Bq, given intake type l and data, and 6) the Bayesian posterior average value of the intake amount squared given intake type l and data.

Our method uses the first data point only as a baseline defining the first time interval, so the sum of the M's in Table 5 is 36 even though there are 37 data points.

The intake probability $P(\text{intake})$ is given by

$$P(\text{intake}) = \sum_l P(\text{intake}|l, y)P(l|y). \tag{44}$$

Table 5: Calculated intakes

Intake date	M	P(intake)	l	χ^2/M	$P(l\|y)$	P(intake$\|l,y$)	$E(x\|l,y)$	$E(x^2\|l,y)$
6/9/1945	9	0.542	iys	1.263	0.1275	0.5504	8.135	166.4
			iym	1.283	0.2485	0.5387	13.65	507.4
			iyl	1.323	0.1149	0.5014	24.02	1882
			iws	1.256	0.127	0.5487	5.927	86.31
			iwm	1.259	0.1274	0.5502	7.025	122.6
			iwl	1.258	0.1273	0.5498	6.506	104.5
			iee	1.262	0.1275	0.5504	8.091	164.5
5/8/1971	2	0.999	iys	2.171	0.0123	0.9902	80.25	7207
			iym	1.456	0.0383	0.9937	95.66	10050
			iyl	0.881	0.0386	0.9969	80.77	7089
			iws	0.790	0.3035	0.9996	4.724	24.24
			iwm	0.730	0.2924	0.9996	6.111	40.54
			iwl	0.660	0.3145	0.9996	6.112	40.52
			iee	7.519	0.0005	0.7583	181.8	53370
3/21/1972	25	1	iys	3.189	1.372E-09	0.5013	6.201	84.69
			iym	3.046	3.711E-09	0.6313	15.86	434.8
			iyl	2.259	1.178E-07	0.9942	73.73	5721
			iws	1.039	0.7056	1	12.32	155
			iwm	1.118	0.2293	1	15.55	247.1
			iwl	1.224	0.0651	1	14.95	228.5
			iee	3.423	8.357E-10	0.1814	1.857	22.02

Similarly, if D_l denotes a dose conversion factor (for example, relating intake x to CEDE for intake type l), then the Bayesian posterior average dose d and its standard deviation are given by

$$\begin{aligned} d &= \sum_l D_l E(x|l,y) P(l|y) \qquad (45) \\ \sigma_d &= \sqrt{\sum_l D_l^2 E(x^2|l,y) P(l|y) - d^2}\,. \end{aligned}$$

We note from Table 5 that the first intake has a probability of only 0.54 and so it might be considered marginal. Setting the limiting intake probability to a higher value such as 90% rather than 50% would eliminate this intake. The other two intakes are quite probable, with probabilities of nearly 1.

To compare our interpretation of this data with the current "standard" method is problematical, since the "standard" method is highly subjective. For example, the fourth data point is 2.4 standard deviations from zero, and an internal dosimetrist might associate this data point with an intake in the time interval preceding this high data point. However our algorithm shows less than 2% probability that this is the case (if the limiting probability for an intake is taken as 2%, an intake still is not calculated in this interval). Also the second intake, involving data points 11 and 12, might be overlooked, even though our analysis shows it to be quite probable.

Obviously internal dosimetry is not a precise science. It is our intention to move it more in the direction of science rather than art. An advantage of our approach is that it is "algorithmic" with stated parameters. Subjectivity and professional judgment ("art") then become explicit in the choice of these parameter values.

We plan to undertake Monte Carlo studies of the accuracy of the unfolding algorithm using simulated data for various assumed intake scenarios. We then will be able to state the accuracy of this approach and investigate the sensitivity to choice of parameters.

C Appendix-Multiplicative factor to express uncertainty

The situation can arise where an intake is known with high probability to have occurred, while the associated dose is very uncertain. As an alternative to expressing a result referring to a positive quantity like dose as

$$x \pm \sigma, \qquad (46)$$

where σ may exceed x, we can express uncertainties as a multiplicative factor. A simple way to do this is to assume that the distribution of the positive quantity

x is approximately log normal, with standard deviation of the logs given by σ_l and mean μ. In terms of these parameters, the mean and standard deviation are given by [21]

$$\begin{aligned} x &= \exp(\mu + \sigma_l^2/2) \\ \sigma &= x\sqrt{\exp(\sigma_l^2) - 1}. \end{aligned} \tag{47}$$

Thus an indication of the uncertainty of x might be expressed as $\times \div f_{ln}$, where

$$f_{ln} = \exp(\sigma_l) = \exp\sqrt{\log(1 + (\sigma/x)^2)}. \tag{48}$$

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